PATENT
PC7250MEB

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: : EXAMINER: J. BROWN
DOUGLAS J. M. ALLEN ET AL. :
SERIAL NO.: 07/449,961 : ART UNIT: 183
FILED: DECEMBER 11, 1989 :
FOR: AZITHROMYCIN DIHYDRATE :

I hereby certify that this correspondence is being deposited with the United States Postal Service as First Class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on this 1st day of December 19 92
Jerome A. Forcier

Hon. Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

DECLARATION UNDER 37 C.F.R. 1.132

I, George A. Forcier, declare that:

1. I received a Ph.D. degree in Analytical Chemistry from the University of Massachusetts in 1966.

2. I have been employed by Pfizer Inc, the assignee of the above-identified application since 1966. My current position is that of Group Director, Analytical Research and Development Department. Part of my responsibility is the supervision and direction of analytical procedures performed on experimental pharmaceuticals, including azithromycin.

3. I am familiar with the subject matter of the above-identified application.

4. I am familiar with the impact which the physical and chemical properties of experimental drugs have on the commercial potential of the product.

5. Hygroscopicity tests on azithromycin dihydrate (Type A) and azithromycin "monohydrate" (Type B) were performed under my direction and supervision. Azithromycin "monohydrate" is a crystalline solid that exists as a non-stoichiometric hydrate because of its hygroscopic nature. The dihydrate (Type A) is a discrete crystalline compound.

6. Example 1, p. 7 of the above-identified application correctly describes the hygroscopic behavior of azithromycin dihydrate at relative humidity of 18%, 33%, 75% and 100%. This experiment was done under my direction and supervision.

7. Preparation 1, p. 9 of the above-identified application correctly describes the hygroscopic behavior of

azithromycin monohydrate at relative humidities of 18%, 33%, 75% and 100%. This experiment was done under my direction and supervision.

8. The significance of Example 1 and Preparation 1 lies in the fact that azithromycin dihydrate maintained the constant water content of the dihydrate (4.6%) at relative humidities of 33% and 75% over a 3 day period. In contrast, the monohydrate increased water content from the theoretical value of 2.6% to 6.6% at 75% relative humidity and 5.6% at 33% relative humidity.

9. A side by side test comparing the relative hygroscopicity of azithromycin dihydrate and monohydrate was conducted under my supervision and direction. Two lots of monohydrate were compared with two lots of dihydrate at 75% relative humidity for 120 hours. The monohydrate was found to gain about six times more water than the dihydrate as shown in the table below.

HYGROSCOPICITY OF AZITHROMYCIN
AT 75% RELATIVE HUMIDITY
Weight Gain (%)

Time (hour)	Monohydrate Lot 209-1F	Dihydrate* Lot 76-1	Dihydrate Lot 274-1	Monohydrate Lot 82-I
0	0.00	0.00	0.00	0.00
2	0.94	- 0.21	0.21	1.58
5	1.04	- 0.20	0.35	1.72
24	1.28	- 0.11	0.39	1.86
48	1.26	- 0.06	0.34	1.81
70	1.25	+ 0.06	0.34	1.81
120	1.13	- 0.20	0.19	1.69

*The weight loss is believed to be due to mechanical loss of very fine powder of this sample when the weighing bottles were opened and closed.

10. Lack of hygroscopicity is an important advantage in a pharmaceutical product. Hygroscopic azithromycin (Type B) has poor handling properties, such as poor flowability and adhesiveness to equipment surfaces, and is susceptible to

water content changes during processing and storage at ambient conditions. Accretion of even small amounts of water often makes formulation difficult or impossible because of these poor handling properties and an inability to place a constant amount of active ingredient in each tablet or capsule.

11. The lack of hygroscopicity of azithromycin dihydrate was an important consideration in selecting this material for commercialization.

12. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: March 19, 1997

George A. Forcier

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